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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,325	06/27/2007	James Russell	RUSSELL-5	9433

1444 7590 11/05/2010

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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
11/05/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,325	RUSSELL ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,8,9,11,14,17,24 and 25* is/are pending in the application.

4a) Of the above claim(s) *24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,8,9,11,14 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0810*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This action is responsive to the Response and Amendment filed August 27, 2010. Claims 1-2, 6, 8-9, 11, 14, and 24-25 have been amended and claims 4-5, 7, 10, 12-13, 15-16, 26-27, 29-30, and 34-36 have been canceled. All prior rejections of claims 4-5, 7, 10, 12-13, and 15-16 are moot in view of the cancellation of those claims. Claims 1-2, 6, 8-9, 11, 14, and 17 remain under consideration and claims 24-25 remain withdrawn (see paragraphs 3-4 below). Applicant's amendments and arguments have been thoroughly reviewed, and are persuasive in part. Particularly, applicant's amendments have overcome prior rejections of claims under 35 USC 112, second paragraph by removing language identified as indefinite, and the amendment of claim 1 to require the use of "a nucleic acid sample from the subject" is sufficient to overcome the prior rejection under 35 USC 101. However, applicant's amendments and arguments are not persuasive with regard to enablement of the claimed invention, and have also necessitated the new grounds of rejection set forth below. Any rejections and/or objections not reiterated in this action have been withdrawn. **This action is FINAL.**

It is noted that the ADS and substitute oath/declaration filed August 27, 2010 have been reviewed and entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

3. Applicant's election with traverse of Group I in the reply filed on January 14, 2010 is again acknowledged. All claims corresponding to Groups III-IV have now been canceled.

The still pending Group II claims, claims 24-25, have been amended such that the claims now require "determining a prognosis in accordance with claim 1" (see text of claim 24, from which claim 25 depends). As claim 1 is not allowable, rejoinder of claims 24-25 (as discussed in MPEP 821.04) is not yet under consideration. However, as a courtesy to applicant, it is noted that claim 24 as written does not appear to require all the limitations of claim 1. Particularly, the claim does not clearly require a method comprising determining a prognosis by performing the method of claim 1, but rather states "determining a prognosis in accordance with claim 1" (such that it is unclear whether the particular method specified in claim 1 must actually be performed to meet the requirements of claims 24-25). Thus, if applicant wishes for claims 24-25 to be eligible for rejoinder (if claim 1 is ultimately allowed), claims 24-25 should be amended such that the clearly require all the limitations of claim 1.

4. Claims 24-25 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 14, 2010.

Specification

5. The amendment filed August 27, 2010 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

a. applicant's amendment at page 44 to recite "more DAF" in lieu of the previously recited "fewer DAF"; and

b. applicant's amendment at page 44 to delete the recitation "A5318C" in the phrase "there was no significant association between the htSNPs G5110A, A5318C, or A6235G and 28-day mortality or multiple system organ failure".

With regard to (a), Applicant's reply of August 27, 2010 characterizes the amendment as a "clerical error" and an "inadvertent error," and states that "That this was a clerical error is supported by the consistency of the corrected language with the remainder of the specification and drawings," pointing specifically to Figure 6 and to other statements on page 44 pertaining to other conditions (respiratory failure, etc.)(see top of page 16 of the reply of August 27, 2010). These arguments have been thoroughly considered but are not persuasive. As was noted in the prior Office action of March 16, 2010, the text at page 44 and the content of Figure 6 do appear contradictory. However, while the reply characterizes the text of page 44 as including a clerical error, it would not have been apparent to one of ordinary skill in the art whether the text at page 44 or the Figure itself contained the error. The other statements referenced by applicant in support of the amendment pertain to different conditions (not

to the relevant condition of cardiovascular failure); thus, the specification includes one source of information indicating one type of association and one other source of information indicating the opposite association (not, e.g., a body of different data in support of one association and a single contradictory statement). An ordinary artisan could not have known that it was applicant's statements at page 44 (as opposed to Figure 6 itself) that contained an error. As discussed in MPEP 2163.07:

> An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction. *In re Oda*, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971).

In the present case, while it was clear that Figure 6 and the description thereof on page 44 were in contradiction with one another (such that the presence of some type of error was clear), the actual identity of the error was not obvious, nor was the nature of the required correction. (It is also noted that both panels of Figure 6 appear to be in contradiction with the text at page 44, but applicant has only amended the characterization of the first panel). Accordingly, the amendment introduces new matter.

With regard to (b), the reply at page 13 states that the inclusion of "A5318C" in the recitation on page 44 at lines 13-14 was also a "clerical error." The reply states that "There is ample support on pages 43 and 44 and in Figures 5 and 6 for a significant association between A5318C and 28 day mortality and DAF of both cardiovascular and respiratory dysfunction". It is noted that the statement in question pertains to "28-day mortality or multiple system organ failure" (not DAF of cardiovascular and respiratory dysfunction); thus, the pertinent disclosures in the specification are those related to 28

day mortality and multiple system organ failure. Regarding 28 day mortality, it is noted that multiple populations are discussed at pages 43-44 of the specification, and that the specification at page 43 does reference a "significant" association between the 5318A allele and 28 mortality in "patients who had sepsis or septic shock" (see lines 15-22 of page 43). However, the amended statement at page 44 does not specify a particular population, and could as readily be interpreted as a statement regarding the larger population (and the lack of any significant association therein) as regarding the smaller 130 patient population (i.e., it is not in fact clear that the statement at lines 13-14 of page 44 includes a typographical error). Further, while page 44 at lines 1-2 does state that 'The 5318 A allele was associated with few days alive and free of multiple-system organ failure," there is no disclosure of a p-value (as with the other disclosures in the same paragraph) or even a statement that the association was "significant". Thus, one of ordinary skill in the art would not have recognized the statement at lines 13-14 of page 44 as containing an obvious error (nor would any correction therefore have been apparent). Further, as the amendment modifies the nature of the disclosures in the specification with respect to the A5318C SNP, the deletion of the reference to this SNP at page 44 introduces new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

6. Claims 1-2, 6, 8-9, 11, 14, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S AMENDMENTS:

Claims 1-2, 6, 8-9, 11, 14, and 17 are indefinite because it is unclear whether the claims as amended are drawn to methods for determining a prognosis for any "inflammatory condition" as referenced in the preamble of claim 1, or to methods of determining a "subject's ability to recover from the inflammatory condition which is SIRS, sepsis or septic shock" as set forth in the body of claim 1. As the language of the preamble and of the body of the claim differ in scope and appear to require different criteria, it is unclear what must in fact be accomplished in order for the requirements of the claim to be met (e.g., what activities would/would not infringe the claims?). Accordingly, clarification is required. It is noted that claim 17 is further indefinite because claim 1 references multiple "inflammatory conditions" and it is unclear whether claim 17 is further limiting of the "inflammatory condition" of the preamble, the method steps, or both.

Claims 1-2, 6, 8-9, 11, 14 and 17 are also indefinite over the use of the relative terms "decreased ability" and "increased ability" in claim 1 (b), as the language of the claim does not clearly indicate with what a comparison is made in measuring or determining an "increase" or "decrease".

Claim Rejections - 35 USC § 112, first paragraph

7. Claims 1-2, 6, 8-9, 11, 14, and 17 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons given in the prior Office action of March 16, 2010.

It is first noted that applicant has amended the specification to modify the content of the disclosure at page 44 and thereby eliminate some of the contradictory statements noted in the Office action at page 15. Thus, the amendments to the specification (while introducing new matter) do obviate some aspects of the rejection set forth in the prior Office action, as the amended version of page 44 reports data that more consistently supports a conclusion that 5318A and 4007C are "risk" alleles or genotypes. Additionally, applicant's amendment limiting the claims to human subjects is acknowledged. However, the remaining grounds of rejection set forth in the prior Office action continue to apply to the claims as amended, and the claims remain rejected for lack enablement for reasons already made of record.

The response traverses the rejection on the following grounds.

(a) The reply argues that the claims have been limited to human subjects and to the inflammatory conditions of SIRS, sepsis, and septic shock, citing definitions of SIRS and sepsis provided in the specification (at page 22) and in the newly cited reference Bone et al. These arguments have been considered, and it is again acknowledged that the claims are now limited to human subjects. However, the claims as presently written are not in fact clearly limited to SIRS, sepsis and septic shock, for the reasons noted above. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re*

Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). It is also noted that the definiteness of the terms SIRS, sepsis and septic shock is not in dispute; rather, the specification lacks sufficient evidence that the claims (including embodiments directed to SIRS, sepsis and septic shock) are enabled, for the totality of the reasons given (see also the further response to arguments below).

(b) At the bottom of page 15 bridging to the top of page 16, the reply includes a discussion of the above-referenced amendments to the specification that eliminate some of the contradictory statements noted in the original rejection. While the amendments do render the specification more consistent with regard to support for a significant association between the 5318A allele and fewer DAF of cardiovascular failure (and therefore an association with "risk"), the amendments do not alter the fact that data in the specification remains limited to findings obtained in a single small population, which (as discussed in the original rejection) would be recognized by one of skill in the relevant art as insufficient to establish a true genetic association. Accordingly, these arguments are also non-persuasive.

(c) At pages 16-17, the reply discusses the cited Dahlman reference, arguing that the standard for enablement applied in the rejection is not proper. The reply states that "it appears that the Office objects to the data in the present application as not properly correlated with the claimed subject matter." The reply then discusses correlations between *in vitro* or *in vivo* animal models and human diseases, citing *In re Brana* and noting that "if the art recognizes that a particular model is correlated with a specific human condition, then it should be accepted unless the Examiner can provide

evidence that the model does not correlate". The reply concludes with arguments that "There is no basis for doubting Applicant's data and conclusions therefrom that support the present claims". These arguments have been thoroughly considered but are not persuasive. The rejection does not allege any lack of correlation between data determined in an *in vitro* or *in vivo* model (either well established or otherwise) and methods practiced in human subjects. In fact, the prior Office action acknowledged that the specification discloses data obtained by directly assaying human subjects; in many art areas, such data would be considered superior to data obtained using an *in vitro* or *in vivo* model, and would be accepted as supporting enablement of a claimed invention (at least with respect to claims limited to the same type of subject [e.g., human subjects when data is reported for such subjects] and the same type of condition(s) [e.g., diagnosis of sepsis if the subjects assayed included a population with sepsis, etc.]). However, in determining whether a claimed invention is or is not enabled, the nature of the invention, the state of the prior art, and the level of predictability of the art must be considered (and were considered in the present case; see pages 12-13 of the prior Office action). The present claims are directed to methods in which the presence of a particular genotype is relied upon in determining a prognosis; thus, the nature of the invention is such that the teachings of the specification and/or the art must support the existence of an actual association between the genotype(s) and the condition(s) for which a prognosis is being determined. As was discussed in the prior Office action, the state of the art with respect to genetic association studies (which is the general art area most relevant to the present claims) teaches a requirement for replication of genetic

associations in multiple populations before it is concluded that a true association is present. The high level of unpredictability in this art area is well known to those of skill in the relevant art (as was exemplified by Dahlman; it is noted that the Dahlman reference was cited as – and is considered to be - exemplary of the art in this particular area). Further, the prior art as exemplified by Dahlman teaches that the number of subjects assayed by applicants would be considered inadequate (by a skilled artisan) to conclude that a true genetic association is present in the instant case. Further, it is reiterated that the prior art with respect to the particular gene of the claims and one of the polymorphisms in question is contradictory and confusing, as was discussed at pages 16-17 of the original rejection, further supporting a conclusion that a single study on a single small group of subjects (as reported in the instant specification) cannot reasonably be relied upon to establish enablement of the invention being claimed. The totality of the evidence in the present case instead supports a need for further data and/or further confirmatory evidence supporting the successful use of the claimed invention in determining a prognosis for an inflammatory condition (including the conditions of SIRS/sepsis/septic shock) in a human subject. Thus, while applicant's arguments regarding correlations have been reviewed and considered, these arguments are not persuasive in establishing enablement of the claimed invention.

(d) In addition to the "Response" to the enablement rejection at pages 15-17 of the reply, the reply includes several short comments in the summary of the rejection itself (at pages 10-14). With regard to the C1418T polymorphism, it is again noted that this polymorphism and disclosures in the art related thereto are considered relevant

because this polymorphism corresponds to the polymorphism described by applicant as being located at position 4007 of SEQ ID NO: 1. The cited prior art has not been applied against the claims in a prior art rejection because this prior art does not teach or suggest the claimed invention (which requires determining a prognosis for a subject who has or is at risk of developing an inflammatory condition wherein a genotype determined indicates a subject's ability to recover from the condition (which may be SIRS, sepsis or septic shock)); rather, the combined teachings of the specification and of the prior art suggest that the claimed invention lacks enablement, for the reasons of record. Applicant's other comments (regarding the amendments to the claims and the specification [including correction of "clerical errors"], and the alleged limitation of the claims to SIRS, sepsis, and septic shock) are addressed above.

As applicant's arguments are not persuasive, the rejection of claims 1-2, 6, 8-9, 11, 14 and 17 for lack of enablement is maintained.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANT'S AMENDMENTS:

8. Claims 1 and 6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

This rejection applies to claim 1 to the extent that claim 1 is drawn to the embodiment of claim 6. Claim 6 has been amended to require "further comprising

determining the sequence of thrombomodulin in the subject". This language is interpreted as encompassing (a) determining the sequence of thrombomodulin (i.e., the protein thrombomodulin, as this is the literal, plain meaning of this claim language) and determining the sequence of the thrombomodulin gene (as the specification clearly references the sequencing of "thrombomodulin" when referencing the thrombomodulin gene). While the specification clearly discloses the sequencing of the thrombomodulin gene, applicant's amendment introduces new matter because the specification does not in fact disclose sequencing of thrombomodulin *per se*. It is noted that the specification does not in fact re-define the term "thrombomodulin" as meaning the thrombomodulin gene, and also clearly references the fact that "thrombomodulin" (i.e., the protein) is encoded by an "intronless gene" (page 1), consistent with the plain meaning of the claim as it would be interpreted by one of ordinary skill in the art. Accordingly, claims 1 and 6 embrace new matter to the extent that the claims encompass methods requiring determining the sequence of thrombomodulin itself, as the originally filed specification does not disclose such methods.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 8:30 am-2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571/272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634